UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,417	12/22/2004	Patrick Cornelis Nicolaas Rensen	101137-60	7547

27387 7590 02/18/2010

LONDA, BRUCE S.
NORRIS MCLAUGHLIN & MARCUS, PA
875 THIRD AVE, 8TH FLOOR
NEW YORK, NY 10022

EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
02/18/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,417	RENSEN ET AL.	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-20 and 22-34* is/are pending in the application.

4a) Of the above claim(s) *19,20,29 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,22-28,30-32 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. The amendment of November 30, 2009 has been entered. Claims 1-16 and 21 are cancelled. Claims 19-20, 29 and 33 are withdrawn. Claim 34 has been newly added. Claims 17-18, 22-28, 30-32 and 34 are under consideration in this office action.

Withdrawal of Objections

2. The objection of claims 17 and 32 have been withdrawn in view of applicants' amendments and arguments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 17-18, 22-28, 30-32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dasseux et al., (WO 99/16458 published April 8, 1999) in view of Rozek et al., (Biochemistry. 1995. Vol. 34, pages 7401-7408).

The claims are drawn to a method for treating a mammal suffering from or is at risk of

developing sepsis or septic shock comprising administering to such mammal a therapeutically effective amount of a peptide and pharmaceutically acceptably adjuvants where the peptide comprises an amino acid sequence selected from SEQ ID NO:11, SEQ ID NO:2 and SEQ ID NO:1.

Dasseux et al, teach apolipoprotein A-1 agonist compositions for treating disorders such as septic shock (page 1, lines 5-9). Dasseux et al, teach the desire to mimic the activity ApoA-I with specific activities such as activation of LCAT approaching that of the native molecule (page 17, lines 17-21). Dasseux et al, teach the ApoA-I agonist are peptides that form amphipathic helices in the presence of lipids, bind lipids, form pre-B-like or HDL-like complexes, activate LCAT, increase serum levels of HDL fractions and promote cholesterol efflux (page 17, lines 20-27). Dasseux et al, teach the peptide design is based on the helical structure and amphipathic properties of 22 amino acid consensus sequence derived from the helical repeats of ApoA-I (page 17, lines 28-32). Dasseux et al, teach the having negative charges being distributed on the rest of the hydrophilic face of the peptide (page 33, lines 25-29). Dasseux et al, the agonist can be used to treat any animals, especially mammals, including humans for enotoxemia which results in septic shock (page 78, lines 9-20). It is noted that sources of sepsis or septic shock can be caused by gram-negative or gram-positive bacteria. Dasseux et al, teach administering the peptide by any suitable route to ensure bioavailability (page 83, lines 30-36) and pharmaceutical formulations including a wide variety of pharmaceutically acceptable adjuvant carriers (page 76, lines 24-32). However Dasseux et al, do not teach administering SEQ ID NO:1, 2 or 11.

Rozek et al., teach apolipoprotein C-I (ApoC-I) is an exchangeable apolipoprotein distributed mainly in HDL and VLDL, where HDL facilitates the uptakes of cholesterol (page 1858, col.1). Rozek et al., teach that LCAT is primarily activated by ApoA-I, whereas ApoC-I serves as the secondary activator and stimulates LCAT activity up to 78% as effectively as ApoA-I (page 1858, col.2). Rozek et al., teach ApoA-I having affinity for lipids (page 1859, col.1). The main structural motif which facilitates the interaction of the exchangeable apolipoprotein with lipids is the amiphipathic helix which is defined as an a-helix with opposing polar and nonpolar faces (page 1859, col.1). Rozek et al., notes that Rozek et al., (Biochemistry 1995, Vol. 34:7401-7408) disclose peptides corresponding to the lipid binding domain of ApoC-I and is characterized by repeating amino acid motifs of 22 resides which form the amphipathic helical structure when associated with lipids (Rozek et al., (Biochemistry 1995, Vol. 34:7401). Furthermore ApoC-I directly increases HDL serum levels. Rozek et al., teach the hydrophobic side chains are exclusively on the concave face, forming two hydrophobic clusters; there are positively charged side chains at the interface of the peptide and the negatively charged side chains are located on the hydrophilic face of the molecules (page 1863-4, col.2-2). Furthermore, Rozek et al., disclose peptides comprising amino acid sequences from SEQ ID NO:11, 2 and 1.

Therefore it would have been prima facie obvious at the time of applicants' invention to apply the peptide comprising the amino acid sequence as taught by Rozek et al., into the method for treating a mammal suffering from or is at risk of developing sepsis or septic shock comprising administering a therapeutically effectively amount of a

peptide and pharmaceutically acceptably adjuvants as taught by Dasseux et al., in order to provide an apolipoprotein A-I agonist composition for treating endotoxemia or septic shock. One of ordinary skill in the art would have a reasonable expectation of success by including ApoC-I peptide within the composition of method of treating sepsis or shock because the art teaches the using peptides that mimic the activity ApoA-I such as activators of LCAT and Rozek et al., teach the ApoC-I peptide has said activation ability. Furthermore, no more than routine skill would have been required to include the ApoC-I peptide because Rozek et al., teach that the ApoC-I peptide forms amphipathic helices in the presence of lipids, bind lipids with its lipid binding domains, increases serum levels of HDL fractions and promotes cholesterol efflux, just as required of an ApoA-I agonist. Finally all of the claimed elements, such as the peptides qualify as ApoA-1 agonist and peptides comprising SEQ ID NO:1, 2, or 11, were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

4. Claims 17-18, 22-28, 30-32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dasseux et al., (US Patent 6,004,925 published December 21, 1999) in view of Rozek et al., (Biochemistry. 1995. Vol. 34, pages 7401-7408).

The claims are drawn to a method for treating a mammal suffering from or is at risk of developing sepsis or septic shock comprising administering to such mammal a

therapeutically effective amount of a peptide and pharmaceutically acceptably adjuvants where the peptide comprises an amino acid sequence selected from SEQ ID NO:11, SEQ ID NO:2 and SEQ ID NO:1.

Dasseux et al, teach apolipoprotein A-1 agonist compositions for treating disorders such as septic shock (col. 2, lines 55-5). Dasseux et al, teach the desire to mimic the activity ApoA-I with specific activities such as activation of LCAT approaching that of the native molecule (col. 11, lines 50-55). Dasseux et al, teach the ApoA-I agonist are peptides that form amphipathic helices in the presence of lipids, bind lipids, form pre-B-like or HDL-like complexes, activate LCAT, increase serum levels of HDL fractions and promote cholesterol efflux (col. 11, lines 55-60). Dasseux et al, teach the peptide design is based on the helical structure and amphipathic properties of 22 amino acid consensus sequence derived from the helical repeats of ApoA-I (col.11, lines 61-67). Dasseux et al, teach the having negative charges being distributed on the rest of the hydrophilic face of the peptide (col. 20 lines 48-53). Dasseux et al., teach pharmaceutical formulations containing ApoA-I agonist and their use to treat diseases associated with endotoxemia, i.e., septic shock (col. 12, lines 14-21).Dasseux et al, the agonist can be used to treat any animals, especially mammals, including humans for enotoxemia which results in septic shock (col. 49, lines 47-59). It is noted that sources of sepsis or septic shock can be caused by gram-negative or gram-positive bacteria. Dasseux et al, teach administering the peptide by any suitable route to ensure bioavailability (col. 52, lines 46-67) and pharmaceutical formulations including a wide

variety of pharmaceutically acceptable adjuvant carriers (col. 48, lines 59-68). However Dasseux et al, do not teach administering SEQ ID NO:1, 2 or 11.

Rozek et al., teach apolipoprotein C-I (ApoC-I) is an exchangeable apolipoprotein distributed mainly in HDL and VLDL, where HDL facilitates the uptakes of cholesterol (page 1858, col.1). Rozek et al., teach that LCAT is primarily activated by ApoA-I, whereas ApoC-I serves as the secondary activator and stimulates LCAT activity up to 78% as effectively as ApoA-I (page 1858, col.2). Rozek et al., teach ApoA-I having affinity for lipids (page 1859, col.1). The main structural motif which facilitates the interaction of the exchangeable apolipoprotein with lipids is the amiphipathic helix which is defined as an a-helix with opposing polar and nonpolar faces (page 1859, col.1). Rozek et al., notes that Rozek et al., (Biochemistry 1995, Vol. 34:7401-7408) disclose peptides corresponding to the lipid binding domain of ApoC-I and is characterized by repeating amino acid motifs of 22 resides which form the amphipathic helical structure when associated with lipids (Rozek et al., (Biochemistry 1995, Vol. 34:7401). Furthermore ApoC-I directly increases HDL serum levels. Rozek et al., teach the hydrophobic side chains are exclusively on the concave face, forming two hydrophobic clusters; there are positively charged side chains at the interface of the peptide and the negatively charged side chains are located on the hydrophilic face of the molecules (page 1863-4, col.2-2). Furthermore, Rozek et al., disclose peptides comprising amino acid sequences from SEQ ID NO:11, 2 and 1.

Therefore it would have been prima facie obvious at the time of applicants' invention to apply the peptide comprising the amino acid sequence as taught by Rozek

et al., into the method for treating a mammal suffering from or is at risk of developing sepsis or septic shock comprising administering a therapeutically effectively amount of a peptide and pharmaceutically acceptably adjuvants as taught by Dasseux et al., in order to provide an apolipoprotein A-I agonist composition for treating endotoxemia or septic shock. One of ordinary skill in the art would have a reasonable expectation of success by including ApoC-I peptide within the composition of method of treating sepsis or shock because the art teaches the using peptides that mimic the activity ApoA-I such as activation of LCAT and Rozek et al., teach the ApoC-I peptide has said ability. Furthermore, no more than routine skill would have been required to include the ApoC-I peptide because Rozek et al., teach that the ApoC-I peptide forms amphipathic helices in the presence of lipids, bind lipids with its lipid binding domains, increases serum levels of HDL fractions and promotes cholesterol efflux, just as required of an ApoA-I agonist. Finally all of the claimed elements, such as peptides that qualify as ApoA-1 agonist and peptides comprising SEQ ID NO:1, 2, or 11, were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Response to Arguments

5. Applicant's arguments filed November 30, 2009 have been fully considered but they are not persuasive. It is noted that the response argues both the 103 together in

view the rejections use of similar art; therefore the response will address the arguments in kind.

Applicants assert that the ApoC-1 and ApoA-1 molecules differ too much to suggest a similar working mechanism; thus there would have been no motivation to combine the teachings. However the issue is not about the similarity of ApoA-I and ApoC-I; rather the issue is about how ApoC-I meets the qualifications of being an ApoA-I agonist. Contrary to applicants assertion, the prior art teaches the related functions of the apolipoproteins along with peptide design similarities. Dasseux et al, teach the desire to mimic the activity ApoA-I with specific activities such as activation of LCAT approaching that of the native molecule (page 17, lines 17-21). Dasseux et al, teach the ApoA-I agonist are peptides that form amphipathic helices in the presence of lipids, bind lipids, form pre-B-like or HDL-like complexes, activate LCAT, increase serum levels of HDL fractions and promote cholesterol efflux (page 17, lines 20-27). Rozek et al., disclose ApoC-I peptides corresponding to the lipid binding domain of ApoC-I and are characterized by repeating amino acid motifs of 22 resides which form the amphipathic helical structure when associated with lipids; thereby meeting the requirements of ApoA-1 agonist.

Dasseux et al, teach the desire to have ApoA-I agonist having a peptide design based on the helical structure and amphipathic properties of 22 amino acid consensus sequence derived from the helical repeats of ApoA-I (page 17, lines 28-32). Rozek et al., disclose ApoC-I peptides corresponding to the lipid binding domain of ApoC-I and

are characterized by repeating amino acid motifs of 22 resides which form the amphipathic helical structure when associated with lipids.

Therefore the arguments about the differing structural similarities and differences as argued by applicants is irrelevant, since the rejection is based on ApoA-I agonist, and peptides which act as ApoA-I agonist, not about the differences between ApoA-I and ApoC-I. Accordingly, the arguments about the size difference between the apolipoproteins are not persuasive in view of the art teachings.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, applicants have not pointed to any knowledge which was not within the level of ordinary skill at the time of the invention; moreover the rejection does not include knowledge gleaned only from the applicant's disclosure. Rather all knowledge is gained from the teachings of Dasseux et al, and Rozek et al.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by

combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been prima facie obvious at the time of applicants' invention to apply the ApoA-I agonist comprising the amino acid sequence as taught by Rozek et al., into the method for treating a mammal suffering from or is at risk of developing sepsis or septic shock comprising administering a therapeutically effectively amount of a peptide and pharmaceutically acceptably adjuvants as taught by Dasseux et al., in order to provide the desired ApoA-I agonist having all the recited structural qualities taught by Dasseux et al., within a composition for treating endotoxemia or septic shock.

Applicants urge that Rozek et al., do not disclose the fragments that applicants are claiming. However it is noted that the claims recite a peptide comprising an amino acid sequence selected from SEQ ID NO:11, SEQ ID NO:2 and SEQ ID NO:1. Rozek et al., disclose peptides comprising amino acid sequences from SEQ ID NO:11, 2 and 1.

Applicants assert that the Examiners reasoning is based upon the combination these two references, one would come to the conclusion that the properties and functions of ApoA1 and Apical, including the effects of the latter in sepsis, are similar. In response to applicant's argument, the fact that applicant has recognized another

advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Furthermore, the examiner's conclusion is not based upon the similarities of ApoA-I and ApoC-I; rather the Examiner's reasoning is based upon the teachings of Dasseux et al., use of ApoA-I agonist for treating sepsis, along with Dasseux et al., teaching of specific structural qualities need by peptides to be useful agonist and the prior art teachings that Rozek et al., teach peptides encompassing the structural requirements and having the needed abilities to meet the qualifications for being ApoA-I agonist.

Therefore applicants arguments about the differences between ApoA-I and ApoC-I are not persuasive since the rejection is on the grounds that all of the claimed elements, such as the peptides qualifying as ApoA-1 agonist and peptides comprising SEQ ID NO:1, 2, or 11, were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Conclusion

6. No claims allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645